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=> d l138 all hitstr tot

L138 ANSWER 1 OF 19  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2004:589442  HCAPLUS
DN   141:111636
ED   Entered STN:  23 Jul 2004
TI   Hyaluronic acid derivatives as drug carriers
IN   Shimoboji, Tsuyoshi; Nakamura, Teruo; Miyamoto, Hajime; Shiokawa, Rie
PA   Chugai Seiyaku Kabushiki Kaisha, Japan
SO   PCT Int. Appl., 35 pp.
     CODEN: PIXXD2
DT   Patent
LA   Japanese
IC   ICM  A61K047-48
     ICS  A61K038-00; A61P043-00; C08B037-08
CC   63-6 (Pharmaceuticals)
FAN.CNT 1
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
PI   WO 2004060404         A1    20040722    WO 2004-JP4             20040105
         W:  AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB,
             BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR,
             CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG,
             ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU,
             ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ,
             KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN,
             MW, MX, MX, MZ
PRAI JP 2002-380391        A     20021227
CLASS
 PATENT NO.       CLASS  PATENT FAMILY CLASSIFICATION CODES
 --------------   -----  ----------------------------------------------
 WO 2004060404    ICM    A61K047-48
                  ICS    A61K038-00; A61P043-00; C08B037-08
 WO 2004060404    ECLA   A61K047/48K8
AB   A method of regulating the rate of extinction of a hyaluronic
     acid (HA) derivative, comprises changing the percentage of substituent
     introduction into the carboxylic acid of glucuronic acid
     of the HA derivative, or comprises changing the mol. weight of the HA
derivative
```

Further, there is provided a drug conjugate wherein a **hyaluronic acid** derivative having its extinction rate regulated is used as a carrier so as to prolong or control the half-life period of drug in blood.

ST controlled release **hyaluronate** drug conjugate

IT Peptides, biological studies
Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biol. active; **hyaluronic acid** derivs. as drug carriers)

IT Drug delivery systems
(controlled-release; **hyaluronic acid** derivs. as drug carriers)

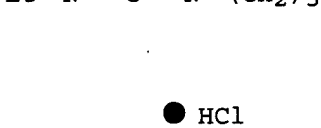
IT 1071-93-8P, Adipic acid **dihydrazide 9004-61-9DP**, **Hyaluronic acid**, reaction products with EDC and adipic **dihydrazide 25952-53-8DP**, EDC (coupling agent), reaction products with **hyaluronate** and adipic **dihydrazide**
RL: **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(**hyaluronic acid** derivs. as drug carriers)

IT **9004-61-9DP**, **Hyaluronic acid**, reaction products with EDC and adipic **dihydrazide 25952-53-8DP**, EDC (coupling agent), reaction products with **hyaluronate** and adipic **dihydrazide**
RL: **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(**hyaluronic acid** derivs. as drug carriers)

RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 25952-53-8 HCAPLUS
CN 1,3-Propanediamine, N'-(ethylcarbonimidoyl)-N,N-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

L138 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2003:719332** HCAPLUS
DN **139:219381**
ED Entered STN: 14 Sep 2003
TI Coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs
IN Hemberger, Juergen; Orlando, Michele
PA Biotechnologie - Gesellschaft Mittelhessen MbH, Germany
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA German
IC ICM A61K047-48
ICS C08B031-18
CC 63-6 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003074087	A1	20030912	WO 2003-EP2083	20030228

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10209821	A1	20030925	DE 2002-10209821	20020306
CA 2478478	AA	20030912	CA 2003-2478478	20030228
EP 1480682	A1	20041201	EP 2003-743359	20030228

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRAI DE 2002-10209821	A	20020306	
WO 2003-EP2083	W	20030228	

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003074087	ICM	A61K047-48
	ICS	C08B031-18
DE 10209821	ECLA	A61K047/48K8; C08B031/00; C08B031/18; C08B031/18B; C08H001/00

AB The invention relates to a method for coupling proteins to a starch-derived modified polysaccharide. The binding interaction between the modified polysaccharide and the protein is based on a covalent bond which is the result of a coupling reaction between the terminal **aldehyde** group or a **functional group** of the modified polysaccharide mol. resulting from the chemical reaction of this **aldehyde** group and a **functional group** of the protein which reacts with the **aldehyde** group or with the resulting **functional group** of the polysaccharide mol. The bond directly resulting from the coupling reaction can be optionally modified by a further reaction to the aforementioned covalent bond. The invention further relates to pharmaceutical compns. that comprise conjugates formed in this coupling process and to the use of said conjugates and compns. for the prophylaxis or therapy of the human or animal body. Thus high (130 kD) and low mol. weight (10 kD) hydroxyethyl starch was selectively oxidized and coupled to various proteins, e.g. human serum albumin, myoglobin, superoxide dismutase, streptokinase, asparaginase.

ST protein polysaccharide coupling drug soly bioavailability biocompatibility

IT Apolipoproteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(B, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Cytokines
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(B-cell growth factor, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Apolipoproteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(E, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Enzymes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Endotoxinase, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Apolipoproteins

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(La, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Cell adhesion molecules
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(RGD, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Venoms
(bee, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Growth factors, animal
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bone-derived, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Neurotrophic factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(brain-derived, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Myoglobins
RL: RCT (Reactant); RACT (Reactant or reagent)
(conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Interleukin 2
Tumor necrosis factors
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Agglutinins and Lectins
Antibodies and Immunoglobulins
Antibodies and Immunoglobulins
Antigens
Blood-coagulation factors
Bone morphogenetic proteins
Ciliary neurotrophic factor
Cytokines
Enzymes, biological studies
Gonadotropins
Growth factors, animal
Growth hormone receptors
Hemoglobins
Hormones, animal, biological studies
Integrins
Lactoferrins
Lipoproteins
Lymphotoxin
Platelet-derived growth factors
Ricins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Biocompatibility

Cation exchange chromatography
Dissolution
Drug bioavailability
Drug delivery systems
Freeze drying
Human
Molecular weight
(coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Interleukin 2
Myoglobins
Polysaccharides, reactions
Tumor necrosis factors
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Human
(human, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Drug delivery systems
(immunotoxins, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Metals, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(ion, oxidation agent; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Polysaccharides, biological studies
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(modified, conjugates with protein drugs; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Oxidation
(of hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Allergens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ragweed, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Albumins, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(serum, human, serum albumin; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Venoms
(snake, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Transforming growth factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(α-, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT Transforming growth factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β-, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT 9061-61-4, NGF 62031-54-3, FGF 62229-50-9, EGF 62683-29-8, Colony stimulating factor
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT 9002-01-1, Streptokinase 9004-10-8, Insulin, reactions 9005-27-0, Hydroxyethyl starch 9007-92-5, Glucagon, reactions 9015-68-3, Asparaginase 9054-89-1, Superoxide dismutase **25952-53-8**, EDC 80029-43-2, 1-**Hydroxybenzotriazole** hydrate 89750-14-1, GLP-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT 9005-27-0DP, Hydroxyethyl starch, oxidized, conjugates with protein drugs
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT 9002-01-1DP, Streptokinase, conjugate with oxidized hydroxyethyl starch 9004-10-8DP, Insulin, conjugate with oxidized hydroxyethyl starch 9007-92-5DP, Glucagon, conjugate with oxidized hydroxyethyl starch 9015-68-3DP, Asparaginase, conjugate with oxidized hydroxyethyl starch 9054-89-1DP, Superoxide dismutase, conjugate with oxidized hydroxyethyl starch 89750-14-1DP, GLP-1, conjugate with oxidized hydroxyethyl starch
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT 50-56-6D, Oxytocin, conjugate with oxidized hydroxyethyl starch 51-48-9D, Thyroxin, conjugate with oxidized hydroxyethyl starch 1393-25-5D, Secretin, conjugate with oxidized hydroxyethyl starch 8001-27-2D, Hirudin, conjugate with oxidized hydroxyethyl starch 9000-96-8D, Arginase, conjugate with oxidized hydroxyethyl starch 9001-01-8D, Kallikrein, conjugate with oxidized hydroxyethyl starch 9001-05-2D, Catalase, conjugate with oxidized hydroxyethyl starch 9001-34-7D, Galactosidase, conjugate with oxidized hydroxyethyl starch 9001-37-0D, Glucose oxidase, conjugate with oxidized hydroxyethyl starch 9001-45-0D, **Glucuronidase**, conjugate with oxidized hydroxyethyl starch 9001-47-2D, Glutaminase, conjugate with oxidized hydroxyethyl starch 9001-62-1D, Lipase, conjugate with oxidized hydroxyethyl starch 9001-99-4D, RNAse, conjugate with oxidized hydroxyethyl starch 9002-07-7D, Trypsin, conjugate with oxidized hydroxyethyl starch 9002-10-2D, Tyrosinase, conjugate with oxidized hydroxyethyl starch 9002-12-4D, Uricase, conjugate with oxidized hydroxyethyl starch 9002-62-4D, Prolactin, conjugate with oxidized hydroxyethyl starch 9002-67-9D, LH, conjugate with oxidized hydroxyethyl starch 9002-68-0D, FSH, conjugate with oxidized hydroxyethyl starch 9002-71-5D, Thyrotropin, conjugate with oxidized hydroxyethyl starch 9002-72-6D, Somatotropin, conjugate with oxidized hydroxyethyl starch 9002-76-0D, Gastrin, conjugate with oxidized hydroxyethyl starch 9003-98-9D, DNAse, conjugate with oxidized hydroxyethyl starch 9003-99-0D, Peroxidase, conjugate with oxidized hydroxyethyl starch 9004-06-2D, Elastase, conjugate with oxidized hydroxyethyl starch 9004-07-3D, Chymotrypsin, conjugate with oxidized hydroxyethyl starch 9007-12-9D, Calcitonin, conjugate with oxidized hydroxyethyl starch 9024-00-4D, Tryptophanase, conjugate with oxidized hydroxyethyl starch 9024-28-6D, Phenylalanineammonium lyase, conjugate with oxidized hydroxyethyl starch 9026-93-1D, Adenosine deaminase, conjugate with oxidized hydroxyethyl starch 9027-69-4D, Adenosine diphosphatase, conjugate with oxidized hydroxyethyl starch 9027-98-9D, conjugate with oxidized hydroxyethyl starch 9028-81-3D, Gluconate oxidase, conjugate with oxidized hydroxyethyl starch 9030-21-1D, Purine nucleoside phosphorylase,

conjugate with oxidized hydroxyethyl starch 9038-70-4D, Somatomedin, conjugate with oxidized hydroxyethyl starch 9039-53-6D, Urokinase, conjugate with oxidized hydroxyethyl starch 9073-78-3D, Thermolysin, conjugate with oxidized hydroxyethyl starch 11000-17-2D, ADH, conjugate with oxidized hydroxyethyl starch 11096-26-7D, Erythropoietin, conjugate with oxidized hydroxyethyl starch 24305-27-9D, Thyroliberin, conjugate with oxidized hydroxyethyl starch 37213-49-3D, α-MSH, conjugate with oxidized hydroxyethyl starch 37228-64-1D, Glucocerebrosidase, conjugate with oxidized hydroxyethyl starch **37259-53-3D**, **Hyaluronidase**, conjugate with oxidized hydroxyethyl starch 39335-03-0D, Glutaminase-asparaginase, conjugate with oxidized hydroxyethyl starch 51110-01-1D, Somatostatin, conjugate with oxidized hydroxyethyl starch 57773-63-4D, Triptorelin, conjugate with oxidized hydroxyethyl starch 80619-01-8D, Bilirubin oxidase, conjugate with oxidized hydroxyethyl starch 89750-15-2D, Glucagon-like peptide II, conjugate with oxidized hydroxyethyl starch 105913-11-9D, Plasminogen activator, conjugate with oxidized hydroxyethyl starch 142243-02-5D, MAP kinase, conjugate with oxidized hydroxyethyl starch 169494-85-3D, Leptin, conjugate with oxidized hydroxyethyl starch 213190-65-9D, Exendin, conjugate with oxidized hydroxyethyl starch
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT 7440-22-4, Silver, reactions 7440-50-8, Copper, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(ion, oxidation agent; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT 25104-18-1, Polylysine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oligolysine, conjugate with oxidized hydroxyethyl starch; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

IT 7553-56-2, Iodine, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(oxidation agent; coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

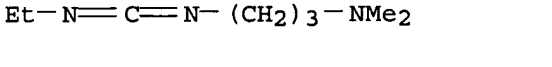
RE

(1) Hemosol Inc; WO 9949897 A 1999 HCAPLUS
(2) Sommermeyer, K; WO 9801158 A 1998 HCAPLUS
(3) Sommermeyer, K; WO 02080979 A 2002
(4) Unilever Nv; DE 2233977 A 1973 HCAPLUS

IT **25952-53-8**, EDC
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

RN 25952-53-8 HCAPLUS

CN 1,3-Propanediamine, N'-(ethylcarbonimidoyl)-N,N-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

IT **37259-53-3D**, **Hyaluronidase**, conjugate with oxidized hydroxyethyl starch
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coupling proteins to a modified polysaccharide, especially oxidized hydroxyethyl starch for use as drugs)

RN 37259-53-3 HCAPLUS
CN Lyase, hyaluronate (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:9653 HCAPLUS
DN 139:207682
ED Entered STN: 07 Jan 2003
TI Preclinical animal studies on INCERT adhesion prevention gel
AU Wiseman, David M.; Sherwood, Charles H.; Sadozai, Khalid K.; **Bulpitt, Paul C.**
CS Synechion, Inc., Dallas, TX, 75248, USA
SO Hyaluronan, [Proceedings of the International Cellucon Conference], 12th, Wrexham, United Kingdom, 2000 (2002), Meeting Date 2000, Volume 2, 17-20. Editor(s): Kennedy, John F. Publisher: Woodhead Publishing Ltd., Cambridge, UK.
CODEN: 69DKVZ; ISBN: 1-85573-570-9
DT Conference
LA English
CC 1-12 (Pharmacology)
AB Cardiac surgery is an area where post-operative adhesions may be particularly problematic. Adhesions forming between the heart, pericardium and sternum may place the mediasternal structures hazardously close to the path of dissection required in a subsequent procedure. Over 360,000 cardiac procedures are performed annually in the United States of which over 10 % (43,000) are re-operations. Complications related to repeat sternal opening arise in approx. 4 % of patients. If hemorrhage does occur during repeat sternotomy the risk of mortality runs at approx. 37 %. Therefore, adhesion formation after cardiac surgery significantly increases the costs and risks of a second cardiac procedure. **Hyaluronan** (HA) is a natural polysaccharide found predominantly in synovial fluid, cartilage and the vitreous humor. Its structure consists of repeating non-sulfated disaccharide units composed of D-**glucuronic acid** and N-acetyl-D-glucosamine. HA has exceptional biocompatibility and has found use in a number of biomedical applications, which include in a number of forms the reduction of post-operative adhesions. Models of pelvic and tendon adhesions have demonstrated that unmodified HA is not effective in reducing adhesions. However, **crosslinked** prepns. of HA may have some benefit. The purpose of this investigation was to determine the efficacy of three HA-based prepns. in a model of pericardial adhesions.
ST **hyaluronan** INCERT gel surgery pericardial adhesion prevention
IT Connective tissue, disease
(adhesion, pericardial; preclin. animal studies on INCERT adhesion prevention **hyaluronan**-based gel)
IT Drug delivery systems
(gels; preclin. animal studies on INCERT adhesion prevention **hyaluronan**-based gel)
IT Heart, disease
Surgery
(post-surgical pericardial adhesion; preclin. animal studies on INCERT adhesion prevention **hyaluronan**-based gel)
IT **510707-52-5**, Seprafilm II
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison; preclin. animal studies on INCERT adhesion prevention **hyaluronan**-based gel)
IT **587840-27-5**, Incert
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preclin. animal studies on INCERT adhesion prevention

hyaluronan-based gel)
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Becker, J; J Am Coll Surg 1996, V183, P297 MEDLINE
(2) Culliford, A; J Thor Cardiovasc Surg 1979, V77, P899
(3) Diamond, M; Fertil Steril 1998, V69, P1067 MEDLINE
(4) Dobell, A; Ann Thorac Surg 1984, V37, P273 MEDLINE
(5) English, T; J Thor Cardiovasc Surg 1978, V76, P56 MEDLINE
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(7) Graves, E; Vital Health Stat 1995, V13(122)
(8) Hagberg, L; J Hand Surg [AM] 1992, V17, P132 MEDLINE
(9) Harada, Y; Thorac Cardiovasc Surg 1988, V96, P193
(10) Johns, D; Development and clinical evaluation of Intergel adhesion prevention solution for the reduction of adhesions following peritoneal cavity surgery 2000, P351
(11) Malm, T; J Thor Cardiovasc Surg 1992, V104, P600 MEDLINE
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(13) Mitchell, J; Eur J Cardiothorac Surg 1994, V8, P149 MEDLINE
(14) Okuyama, N; J Surg Res 1998, V78, P118 HCAPLUS
(15) Wiseman, D; Hazards and Prevention of Postsurgical Pericardial Adhesions 1996, P240
(16) Wiseman, D; J Surg Res 1992, V53, P362 HCAPLUS
IT **510707-52-5**, Seprafilm II
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison; preclin. animal studies on INCERT adhesion prevention **hyaluronan**-based gel)
RN 510707-52-5 HCAPLUS
CN Seprafilm II (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **587840-27-5**, Incert
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preclin. animal studies on INCERT adhesion prevention **hyaluronan**-based gel)
RN 587840-27-5 HCAPLUS
CN Incert (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:732148 HCAPLUS
DN 137:389118
ED Entered STN: 27 Sep 2002
TI Disulfide **Cross-Linked Hyaluronan** Hydrogels
AU Shu, Xiao Zheng; Liu, Yanchun; Luo, Yi; Roberts, Meredith C.; Prestwich, Glenn D.
CS Department of Medicinal Chemistry, University of Utah, Salt Lake City, UT, 84108-1257, USA
SO Biomacromolecules (2002), 3(6), 1304-1311
CODEN: BOMAF6; ISSN: 1525-7797
PB American Chemical Society
DT Journal
LA English
CC 63-7 (Pharmaceuticals)
Section cross-reference(s): 33
AB A new disulfide **crosslinking** strategy was developed to prepare **hyaluronic acid** (HA) hydrogels from thiol-modified HA. First, dithiobis(propanoic **dihydrazide**) (DTP) and dithiobis(butyric **dihydrazide**) (DTB) were synthesized and then coupled to HA with **carbodiimide** chemical Next, disulfide bonds of the initially formed gel were reduced using dithiothreitol (DTT) to give,

after exhaustive dialysis, the corresponding thiol-modified macromol. derivs. HA-DTPH and HA-DT. The degree of substitution of HA-DTPH and HA-DTBH was controlled from 20-7% of available **glucuronate** carboxylic acid groups. The pKa values of the HA-thiol derivs. were determined spectrophotometrically to be pKa 8.87 (HA-DTPH) and pKa 9.01 (HA-DTBH). The thiol groups were oxidized in air to reform disulfide linkages, which resulted in HA-DTPH and HA-DTBH hydrogel films. Further oxidation of these hydrogels with dilute H2O2 created addnl. **crosslinks** and afforded poorly swellable films. The disulfide **crosslinking** was reversible, and films were again reduced to sols with DTT. Release of blue dextran from **crosslinked** films was used as a model for drug release. The rapid gelation of the HA-DTPH solution under physiol. conditions was also achieved, which demonstrated the capacity for in situ cell encapsulation. Thus, L-929 murine fibroblasts were encapsulated in HA-DTPH hydrogel; these cells remained viable and proliferated during 3 days of culture in vitro.

ST disulfide **crosslinked hyaluronan** hydrogel prepn

IT Animal cell line
(L-929; preparation of disulfide **crosslinked hyaluronan** hydrogels)

IT Animal cell
Crosslinking
Drug delivery systems
Fibroblast
Hydrogels
Ionization
Polydispersity
Prosthetic materials and Prosthetics
Swelling, physical
(preparation of disulfide **crosslinked hyaluronan** hydrogels)

IT 50906-77-9P 52821-72-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**crosslinker**; preparation of disulfide **crosslinked hyaluronan** hydrogels)

IT **476197-21-4 476197-23-6 476197-24-7 476197-25-8**
RL: FMU (Formation, unclassified); **RCT (Reactant)**; FORM (Formation, nonpreparative); **RACT (Reactant or reagent)**
(preparation of disulfide **crosslinked hyaluronan** hydrogels)

IT **476197-26-9P 476197-27-0P**
RL: PRP (Properties); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of disulfide **crosslinked hyaluronan** hydrogels)

IT **9004-61-9, Hyaluronan**
RL: **RCT (Reactant)**; THU (Therapeutic use); BIOL (Biological study); **RACT (Reactant or reagent)**; USES (Uses)
(preparation of disulfide **crosslinked hyaluronan** hydrogels)

RE.CNT 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD

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IT **476197-21-4 476197-23-6 476197-24-7 476197-25-8**
RL: FMU (Formation, unclassified); **RCT (Reactant)**; FORM (Formation, nonpreparative); **RACT (Reactant or reagent)**
(preparation of disulfide **crosslinked hyaluronan** hydrogels)

RN 476197-21-4 HCAPLUS
CN Hyaluronic acid, 2-[3-[(3-hydrazino-3-oxopropyl)dithio]-1-oxopropyl]hydrazide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

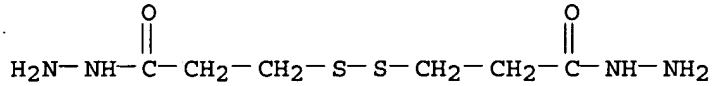
RN 476197-23-6 HCAPLUS
CN Hyaluronic acid, 2-[4-[(4-hydrazino-4-oxobutyl)dithio]-1-

oxobutyl]hydrazide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 476197-24-7 HCAPLUS
CN Hyaluronic acid, polymer with 3,3'-dithiobis[propanoic acid] dihydrazide (9CI) (CA INDEX NAME)

CM 1

CRN 50906-77-9
CMF C6 H14 N4 O2 S2



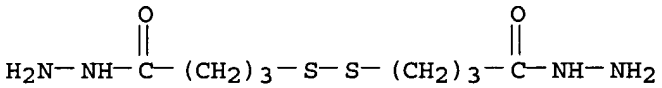
CM 2

CRN 9004-61-9
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 476197-25-8 HCAPLUS
CN Hyaluronic acid, polymer with 4,4'-dithiobis[butanoic acid] dihydrazide (9CI) (CA INDEX NAME)

CM 1

CRN 52821-72-4
CMF C8 H18 N4 O2 S2



CM 2

CRN 9004-61-9
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **476197-26-9P 476197-27-0P**
RL: PRP (Properties); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(preparation of disulfide **crosslinked hyaluronan** hydrogels)
RN 476197-26-9 HCAPLUS
CN Hyaluronic acid, 2-(3-mercapto-1-oxopropyl)hydrazide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 476197-27-0 HCAPLUS
CN Hyaluronic acid, 2-(4-mercapto-1-oxobutyl)hydrazide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9004-61-9, Hyaluronan.**
RL: **RCT (Reactant)**; THU (Therapeutic use); BIOL (Biological study); **RACT (Reactant or reagent)**; USES (Uses)
(preparation of disulfide **crosslinked hyaluronan** hydrogels)
RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:675988 HCAPLUS
DN 137:217172
ED Entered STN: 08 Sep 2002
TI Preparation of thiol-modified disulfide cross-linked **hyaluronan**
IN **Bulpitt, Paul C. A.**; Sherwood, Charles H.; Sadozai, Khalid K.
PA Anika Therapeutics, Inc., USA
SO PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C323-25
ICS C07C323-32; C07C335-08; C07C335-16; C07C323-44; **C08B037-08**; **A61K031-728**; A61P027-02; A61P041-00
CC 33-8 (Carbohydrates)
Section cross-reference(s): 6, 23
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002068383	A2	20020906	WO 2002-US5081	20020221
	WO 2002068383	A3	20030227		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2437417	AA	20020906	CA 2002-2437417	20020221
	US 2002128512	A1	20020912	US 2002-81019	20020221
	US 6620927	B2	20030916		
	EP 1368309	A2	20031210	EP 2002-721085	20020221
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2004038934	A1	20040226	US 2003-640815	20030814
	US 6884788	B2	20050426		
PRAI	US 2001-271023P	P	20010222		
	US 2002-81019	A3	20020221		
	WO 2002-US5081	W	20020221		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002068383	ICM	C07C323-25
	ICS	C07C323-32; C07C335-08; C07C335-16; C07C323-44; **C08B037-08**; **A61K031-728**; A61P027-02; A61P041-00
WO 2002068383	ECLA	C07C323/25D2; C07C323/32; C07C323/44; C07C335/08; C07C335/16; C08B037/00P2F
US 2002128512	NCL	536/123.100; 536/017.200; 536/018.700; 536/055.000; 536/055.100; 536/055.300; 536/106.000

ECLA C07C323/25D2; C07C323/32; C07C323/44; C07C335/08; C07C335/16; C08B037/00P2F
US 2004038934 NCL 514/054.000; 536/053.000
ECLA C07C323/25D2; C07C323/32; C07C323/44; C07C335/08; C07C335/16; C08B037/00P2F
OS CASREACT 137:217172; MARPAT 137:217172
AB The present invention relates to biscarbodiimides, thiourea derivs., urea derivs., and cross-linked **hyaluronan** derivs. having at least one intramol. disulfide bond, and methods of preparation thereof. The invention also includes thiolated **hyaluronan** derivs. and salts thereof having at least one pendant thiol group or a modified pendant thiol group, and methods of preparation thereof. An example of a modified pendant thiol group is a **sulfhydryl** group linked to a small mol. such as a bioactive agent, for example a drug or pharmaceutically active moiety. A **hyaluronan** derivative having a **sulfhydryl** group linked to a pharmaceutically active moiety is useful as a sustained or controlled release drug delivery vehicle. Compns. containing the **hyaluronan** derivs. of the invention are useful in ophthalmic surgery and in tissue engineering.
ST drug delivery **hyaluronan** sulfide thiol prepn polysaccharide uronate carbodiimide
IT Disulfide group
Sulfhydryl group
(Preparation of thiol-modified disulfide cross-linked **hyaluronan**)
IT Polysaccharides, preparation
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(Preparation of thiol-modified disulfide cross-linked **hyaluronan**)
IT Drug delivery systems
(potential; Preparation of thiol-modified disulfide cross-linked **hyaluronan**)
IT Thiols (organic), preparation
Uronic acids
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of thiol-modified disulfide cross-linked **hyaluronan**)
IT 51-85-4, Cystamine 60-24-2, 2-Mercaptoethanol 103-72-0, Phenyl isothiocyanate 128-08-5, N-Bromosuccinimide 590-42-1, tert-Butyl isothiocyanate 592-82-5, Butyl isothiocyanate 603-35-0, Triphenylphosphine, reactions 628-30-8, Propyl isothiocyanate 722-27-0, 4-Aminophenyl disulfide 1141-88-4 3483-12-3, Dithiothreitol 4426-79-3, sec-Butyl isothiocyanate 7440-66-6, Zinc, reactions 16853-85-3, Lithium aluminum hydride 16940-66-2, Sodium borohydride 51805-45-9, TCEP 396077-56-8 455300-09-1 455300-13-7 455300-15-9 455300-17-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(Preparation of thiol-modified disulfide cross-linked **hyaluronan**)
IT **9004-61-9DP, Hyaluronan**, thiol-modified disulfide cross-linked 396077-55-7P 455300-11-5P **457632-30-3P**
RL: **RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)**
(Preparation of thiol-modified disulfide cross-linked **hyaluronan**)
IT **457632-25-6P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(Preparation of thiol-modified disulfide cross-linked **hyaluronan**)
IT 542-85-8, Ethyl isothiocyanate
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of thiol-modified disulfide cross-linked **hyaluronan**)
IT **9004-61-9DP, Hyaluronan**, thiol-modified disulfide cross-linked **457632-30-3P**
RL: **RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)**
(Preparation of thiol-modified disulfide cross-linked **hyaluronan**)

RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 457632-30-3 HCAPLUS
CN Hyaluronamide, N-ethyl-N-[[(2-mercaptoethyl)amino]carbonyl]- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **457632-25-6P**
RL: **SPN (Synthetic preparation)**; **PREP (Preparation)**
(Preparation of thiol-modified disulfide cross-linked **hyaluronan**)
RN 457632-25-6 HCAPLUS
CN Hyaluronamide, N,N'-[dithiobis(2,1-ethanediyliminocarbonyl)]bis[N-ethyl- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:564876 HCAPLUS
DN 135:142300
ED Entered STN: 03 Aug 2001
TI Gel-infused polymeric sponges for tissue repair and augmentation
IN Bentz, Hanne; Garcia, A. Minerva; Hubbell, Jeffrey A.
PA **Orthogene, Inc., USA**
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61L
CC 63-7 (Pharmaceuticals)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001054735	A2	20010802	WO 2001-US2837	20010126
	WO 2001054735	A3	20011220		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 2001034623	A5	20010807	AU 2001-34623	20010126
	US 2003095993	A1	20030522	US 2002-207439	20020726
PRAI	US 2000-178646P	P	20000128		
	WO 2001-US2837	W	20010126		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001054735	ICM	A61L
US 2003095993	NCL	424/426.000
	ECLA	A61L027/38; A61L027/48+C08L89/06; A61L027/48+C08L5/08; A61L027/52; A61L027/56

AB Gel-infused sponge matrix comprising an absorbable sponge material, a gel and an active ingredient are disclosed, as are methods of enhancing tissue repair, regeneration or augmentation using the gel-infused sponge. A sponge material is selected from collagens, polysaccharides, synthetic polymers, or **hyaluronic acid**, while a gel precursor is a fibrinogen, thrombin, or serum albumin. For example, gels of low crosslink d. and/or low protein or gel precursor concentration, that would form

only weak gels by themselves formed a more cohesive and stronger material when added into a sponge and retain enough porosity to be remodeled into the new tissue, such as bone.

ST polymer sponge protein gel tissue repair regeneration; bone cartilage repair sponge gel composite implant

IT Bone morphogenetic proteins
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2; protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)

IT Polymers, biological studies
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biodegradable; protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)

IT Prosthetic materials and Prosthetics
(composites, implants; protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)

IT Bone, disease
(defect; protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)

IT Polyoxyalkylenes, biological studies
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs.; protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)

IT Regeneration, animal
(nerve; protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)

IT Animal tissue
Bone
Buffers
Cartilage
Crosslinking agents
Gelation agents
Gels
Meniscus
Nerve
Physiological saline solutions
Porosity
Regeneration, animal
(protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)

IT Collagens, biological studies
Fibrinogens
Growth factors, animal
Polymers, biological studies
Polysaccharides, biological studies
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)

IT Nerve
(regeneration; protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)

IT Albumins, biological studies
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum; protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)

IT Transforming growth factors
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(β-; protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)
IT 107-15-3, Ethylenediamine, uses
RL: MOA (Modifier or additive use); USES (Uses)
(**hyaluronic acid** modified by; protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)
IT 9002-04-4, Thrombin **9004-61-9**, **Hyaluronic acid**
9067-32-7, **Hyaluronic acid** sodium salt
25322-68-3D, Polyethylene glycol, derivs.
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)
IT **9004-61-9**, **Hyaluronic acid 9067-32-7**
, **Hyaluronic acid** sodium salt
RL: DEV (Device component use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(protein gel-infused biodegradable polymeric sponges for tissue repair and augmentation)
RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9067-32-7 HCAPLUS
CN Hyaluronic acid, sodium salt (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:209960 HCAPLUS
DN 132:256070
ED Entered STN: 31 Mar 2000
TI Functionalized derivatives of **hyaluronic acid** and formation of hydrogels in situ using same
IN **Aeschlimann, Daniel**; **Bulpitt, Paul**
PA UK
SO PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61L024-00
ICS **C08B037-08**; A61L027-00
CC 63-8 (Pharmaceuticals)
Section cross-reference(s): 9, 16, 33
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000016818	A1	20000330	WO 1999-EP6913	19990917
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6630457	B1	20031007	US 1998-156829	19980918 <--
CA 2344215	AA	20000330	CA 1999-2344215	19990917
AU 9961922	A1	20000410	AU 1999-61922	19990917
EP 1115433	A1	20010718	EP 1999-948783	19990917
EP 1115433	B1	20041208		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, SI, LT, LV, FI, RO

	AT 284229	E	20041215	AT 1999-948783	19990917
	US 2004072793	A1	20040415	US 2003-680000	20031006 <--
PRAI	US 1998-156829	A	19980918		
	WO 1999-EP6913	W	19990917		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000016818	ICM	A61L024-00
	ICS	**C08B037-08**; A61L027-00
WO 2000016818	ECLA	C12N005/00S; A61L024/08+C08L5/08; A61L027/20+C08L5/08; C08B037/00P2F
US 6630457	NCL	514/054.000; 435/243.000; 435/253.600; 514/002.000; 514/008.000; 536/053.000
	ECLA	A61L024/08+C08L5/08; A61L027/20+C08L5/08; C08B037/00P2F; C12N005/00S <--
US 2004072793	NCL	514/054.000; 536/053.000
	ECLA	A61L024/08+C08L5/08; A61L027/20+C08L5/08; C08B037/00P2F; C12N005/00S <--

AB Methods for chemical modification of **hyaluronic acid**, formation of **amine** or **aldehyde** functionalized **hyaluronic acid**, and the crosslinking thereof to form hydrogels are provided. Functionalized **hyaluronic acid** hydrogels of this invention can be polymerized in situ, are biodegradable, and can serve as a tissue adhesive, a tissue separator, a drug delivery system, a matrix for cell cultures, and a temporary scaffold for tissue regeneration. **Hyaluronic acid** derivs. prepared include **hydrazideo** di-Me acetal, **aminoacetaldehyde** di-Me acetal, diaminoethane, L-lysine Me ester, and L-histidine Me ester. Examples of formation of crosslinked **hyaluronic acid** hydrogels were given.

ST **hyaluronic acid** deriv hydrogel

IT Adhesives
Adhesives
(biol. tissue; functionalized derivs. of **hyaluronic acid** and formation of hydrogels in situ)

IT **Aldehydes**, biological studies
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates with **hyaluronic acid**; functionalized derivs. of **hyaluronic acid** and formation of hydrogels in situ)

IT Animal tissue culture
Hydrogels
(functionalized derivs. of **hyaluronic acid** and formation of hydrogels in situ)

IT Bone morphogenetic proteins
Growth factors, animal
Peptides, biological studies
RGD peptides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(functionalized derivs. of **hyaluronic acid** and formation of hydrogels in situ)

IT Drug delivery systems
(hydrogels; functionalized derivs. of **hyaluronic acid** and formation of hydrogels in situ)

IT Medical goods
Medical goods
(tissue adhesives; functionalized derivs. of **hyaluronic acid** and formation of hydrogels in situ)

IT Transforming growth factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β-; functionalized derivs. of **hyaluronic acid**

and formation of hydrogels in situ)
IT 262352-91-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(functionalized derivs. of **hyaluronic acid** and
formation of hydrogels in situ)
IT 107-15-3DP, 1,2-Ethanediamine, conjugates with **hyaluronic acid**, biological studies 110-60-1DP, 1,4-Butanediamine, conjugates with **hyaluronic acid** 687-64-9DP, conjugates with **hyaluronic acid** 1071-93-8DP, conjugates with **hyaluronic acid** 1499-46-3DP, conjugates with **hyaluronic acid** **9004-61-9DP**, **Hyaluronic acid**, derivs. 22483-09-6DP, conjugates with **hyaluronic acid** 249913-43-7DP, conjugates with **hyaluronic acid**
RL: PRP (Properties); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(functionalized derivs. of **hyaluronic acid** and
formation of hydrogels in situ)
IT 1071-93-8, Adipic **dihydrazide** 3878-55-5, Monomethyl succinate 7389-87-9, L-Histidine methyl ester dihydrochloride **9067-32-7**, Sodium **hyaluronate** 15467-15-9, 1,2-Ethanediamine hydrochloride 22483-09-6, **Aminoacetaldehyde** dimethyl acetal 26348-70-9, L-Lysine methyl ester dihydrochloride
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(functionalized derivs. of **hyaluronic acid** and
formation of hydrogels in situ)
IT 302-01-2DP, Hydrazine, derivs., preparation 262352-90-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(functionalized derivs. of **hyaluronic acid** and
formation of hydrogels in situ)
IT **80146-85-6**, **Transglutaminase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(substrates for; functionalized derivs. of **hyaluronic acid** and formation of hydrogels in situ)
RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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(4) Pouyani, T; US 5652347 A 1997 HCAPLUS
(5) Seikagaku Kogyo Co Ltd; WO 9718244 A 1997 HCAPLUS
(6) Univ Brown Res Found; WO 9745532 A 1997 HCAPLUS
IT **9004-61-9DP**, **Hyaluronic acid**, derivs.
RL: PRP (Properties); **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(functionalized derivs. of **hyaluronic acid** and
formation of hydrogels in situ)
RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9067-32-7**, Sodium **hyaluronate**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(functionalized derivs. of **hyaluronic acid** and
formation of hydrogels in situ)
RN 9067-32-7 HCAPLUS
CN Hyaluronic acid, sodium salt (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **80146-85-6**, **Transglutaminase**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(substrates for; functionalized derivs. of **hyaluronic acid** and formation of hydrogels in situ)
RN 80146-85-6 HCAPLUS
CN Glutamyltransferase, glutaminylpeptide γ- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:602452 HCAPLUS
DN 131:341857
ED Entered STN: 23 Sep 1999
TI New strategy for chemical modification of **hyaluronic acid**: preparation of functionalized derivatives and their use in the formation of novel biocompatible hydrogels
AU **Bulpitt, Paul**; **Aeschlimann, Daniel**
CS Division of Orthopedic Surgery, H5/301 Clinical Science Center, University of Wisconsin, Madison, WI, 53792, USA
SO Journal of Biomedical Materials Research (1999), 47(2), 152-169
CODEN: JBMRBG; ISSN: 0021-9304
PB John Wiley & Sons, Inc.
DT Journal
LA English
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 33
AB Biodegradable materials for spatially and temporally controlled delivery of bioactive agents such as drugs, growth factors, or cytokines are key to facilitating tissue repair. We have developed a versatile method for chemical **crosslinking** high-mol.-weight **hyaluronic acid** under physiol. conditions yielding biocompatible and biodegradable hydrogels. The method is based on the introduction of **functional groups** onto **hyaluronic acid** by formation of an **active ester** at the carboxylate of the **glucuronic acid** moiety and subsequent substitution with a side chain containing a **nucleophilic** group on one end and a (protected) **functional group** on the other. We have formed **hyaluronic acid** with amino or **aldehyde** functionality, and subsequently hydrogels with these **hyaluronic acid** derivs. and bifunctional **crosslinkers** or mixts. of the **hyaluronic acid** derivs. carrying different functionalities using **active ester**- or **aldehyde**-mediated reactions. Size anal. of the **hyaluronic acid** derivs. showed that the chemical modification did not lead to fragmentation of the polysaccharide. Hydrogels formed with **hyaluronic acid** derivatized to a varying degree and **crosslinked** with low- or high-mol.-weight **crosslinkers** were evaluated for biodegradability by digestion with **hyaluronidase** and for biocompatibility and ectopic bone formation by s.c. implantation in rats. Several hydrogel formulations showed excellent cell infiltration and chondro-osseous differentiation when loaded with bone morphogenetic protein-2 (BMP-2). Synergistic action of insulin-like growth factor-1 with BMP-2 promoted cartilage formation in this model, while addition of transforming growth factor-β and BMP-2 led to rapid replacement of the matrix by bone.
ST **hyaluronic acid** deriv prepn biocompatible hydrogel
IT Bone morphogenetic proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2; preparation of functionalized derivs. and their use in the formation of novel biocompatible hydrogels)
IT Drug delivery systems
(hydrogels; preparation of functionalized derivs. and their use in the formation of novel biocompatible hydrogels)
IT Bone

Crosslinking
Particle size distribution
(preparation of functionalized derivs. and their use in the formation of novel biocompatible hydrogels)

IT Transforming growth factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β-; preparation of functionalized derivs. and their use in the formation of novel biocompatible hydrogels)

IT 333-18-6, Ethylenediamine dihydrochloride 333-93-7, 1,4-Butanediamine dihydrochloride 687-64-9, Lysine methyl ester 1071-93-8, Adipic acid **dihydrazide** 2592-95-2, 1-**Hydroxybenzotriazole** 3878-55-5, Monomethyl succinate 6055-52-3, 1,6-Hexanediamine dihydrochloride **9067-32-7**, Sodium **hyaluronate** 22483-09-6, **Aminoacetaldehyde** dimethyl acetal 82436-78-0, N-**Hydroxysulfosuccinimide**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(preparation of functionalized derivs. and their use in the formation of novel biocompatible hydrogels)

IT 2592-95-2DP, 1-**Hydroxybenzotriazole**, reaction product with **hyaluronic acid** 82436-78-0DP, N-**Hydroxysulfosuccinimide**, reaction product with **hyaluronic acid** 249913-42-6P 249913-43-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of functionalized derivs. and their use in the formation of novel biocompatible hydrogels)

IT 107-15-3DP, Ethylenediamine, reaction product with **hyaluronic acid** 110-60-1DP, 1,4-Diaminobutane, reaction product with **hyaluronic acid** 124-09-4DP, 1,6-Diaminohexane, reaction product with **hyaluronic acid** 687-64-9DP, Lysine methyl ester, reaction product with **hyaluronic acid** 1071-93-8DP, Adipic **dihydrazide**, reaction product with **hyaluronic acid** 22483-09-6DP, **Aminoacetaldehyde** dimethyl acetal, reaction product with **hyaluronic acid** 249913-43-7DP, reaction product with **hyaluronic acid**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of functionalized derivs. and their use in the formation of novel biocompatible hydrogels)

IT 67763-96-6, Insulin-like growth factor-1
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of functionalized derivs. and their use in the formation of novel biocompatible hydrogels)

RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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IT **9067-32-7**, Sodium **hyaluronate**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(preparation of functionalized derivs. and their use in the formation of novel biocompatible hydrogels)
RN 9067-32-7 HCAPLUS
CN Hyaluronic acid, sodium salt (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:136762 HCAPLUS
DN 130:182722
ED Entered STN: 03 Mar 1999
TI Preparation and surface morphology of **hydrazide**-functionalized derivatives of **hyaluronic acids** as hydrogels
IN Prestwich, Glenn D.; Marecak, Dale M.
PA The Research Foundation of State University of New York, USA
SO U.S., 27 pp., Cont.-in-part of U.S. Ser. No. 158,996.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-715
ICS C08B037-00; C07H005-04
INCL 514054000
CC 33-8 (Carbohydrates)
Section cross-reference(s): 34, 66, 75
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 5874417	A	19990223	US 1996-644304	19960510	<--
	US 5616568	A	19970401	US 1993-158996	19931130	<--
	US 5652347	A	19970729	US 1995-484567	19950607	<--
PRAI	US 1993-158996	A2	19931130	<--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
US 5874417	ICM	A61K031-715	
	ICS	C08B037-00; C07H005-04	
	INCL	514054000	
US 5874417	NCL	514/054.000; 514/944.000; 514/950.000; 514/964.000; 536/029.100; 536/055.000; 536/055.100; 536/055.300; 536/123.100	
	ECLA	C08B037/00P2F	<--
US 5616568	NCL	514/054.000; 514/053.000; 536/017.200; 536/018.700; 536/055.000; 536/055.100; 536/055.300; 536/123.100	<--
US 5652347	NCL	536/018.500; 536/123.100; 536/124.000; 536/126.000	
	ECLA	C08B037/00P2F	<--

AB **Hyaluronate peptides** functionalized with a **hydrazide** at **glucuronic acid** sites of said **hyaluronate**, wherein the **hydrazide** is chosen from a group consisting of: **monohydrazide** and **hydrazides** comprising three or more **amine** groups were prepared as hydrogels. Surface morphol. of these compds. was also reported.

ST **peptide hydrazide hyaluronate** prepn hydrogel morphol; **hydrazide hyaluronate** prepn hydrogel surface morphol

IT Hydrogels
Surface structure
(preparation and surface morphol. of **hydrazido**-functionalized derivs. of **hyaluronic acids** as hydrogels)

IT **Peptides, preparation**
Uronic acids
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation and surface morphol. of **hydrazido**-functionalized derivs. of **hyaluronic acids** as hydrogels)

IT **220650-31-7P 220650-32-8P 220650-33-9P**
220650-34-0P 220650-35-1P 220650-48-6P
RL: PRP (Properties); **SPN (Synthetic preparation)**; **PREP (Preparation)**
(preparation and surface morphol. of **hydrazido**-functionalized derivs. of **hyaluronic acids** as hydrogels)

IT 123-46-6, (Carboxymethyl) trimethyl ammonium chloride **hydrazide** 1071-93-8 1126-58-5, 1-(Carboxymethyl) pyridinium chloride **hydrazide 1892-57-5** 2203-97-6, Hydrocortisone-hemisuccinate 4146-43-4 **6066-82-6, N-Hydroxysuccinimide 9004-61-9, Hyaluronic acid** 15687-27-1, Ibuprofen 20247-84-1 29878-26-0 127634-19-9 142702-31-6 142702-32-7
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(preparation and surface morphol. of **hydrazido**-functionalized derivs. of **hyaluronic acids** as hydrogels)

IT 104400-52-4P **220650-37-3P 220650-43-1P**
220650-45-3P
RL: **RCT (Reactant)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**; **RACT (Reactant or reagent)**
(preparation and surface morphol. of **hydrazido**-functionalized derivs. of **hyaluronic acids** as hydrogels)

RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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IT **220650-31-7P 220650-32-8P 220650-33-9P**
220650-34-0P 220650-35-1P 220650-48-6P
RL: PRP (Properties); **SPN (Synthetic preparation)**; **PREP (Preparation)**
(preparation and surface morphol. of **hydrazido**-functionalized derivs. of **hyaluronic acids** as hydrogels)

RN 220650-31-7 HCAPLUS
CN Hyaluronic acid, 2,2'-[(1,8-diimino-1,8-octanediyl)bis[hydrazo(1,6-dioxo-6,1-hexanediyl)]]dihydrazide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 220650-32-8 HCAPLUS
CN Hyaluronic acid, 2-[6-[2-[4-[[(11β)-11,17-dihydroxy-3,20-dioxopregn-4-en-21-yl]oxy]-1,4-dioxobutyl]hydrazino]-1,6-dioxohexyl]hydrazide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 220650-33-9 HCAPLUS
CN Hyaluronic acid, 2,2'-[(1,8-dioxo-1,8-octanediyl)bis[hydrazo(1,6-dioxo-6,1-hexanediyl)]]dihydrazide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 220650-34-0 HCAPLUS
CN Hyaluronic acid, 2,2'-[dithiobis[(1-oxo-3,1-propanediyl)hydrazo(1,6-dioxo-6,1-hexanediyl)]]dihydrazide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 220650-35-1 HCAPLUS
CN Hyaluronic acid, 2,2'-[1,2-ethanediylbis[oxy(1,4-dioxo-4,1-butanediyl)hydrazo(1,6-dioxo-6,1-hexanediyl)]]dihydrazide (9CI) (CA INDEX NAME)

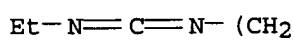
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 220650-48-6 HCAPLUS
CN Hyaluronic acid, 2-[6-[2-[2-[4-(2-methylpropyl)phenyl]-1-oxopropyl]hydrazino]-1,6-dioxohexyl]hydrazide (9CI) (CA INDEX NAME)

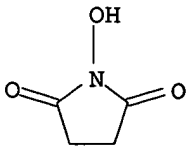
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **1892-57-5 6066-82-6, N-Hydroxysuccinimide 9004-61-9, Hyaluronic acid**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(preparation and surface morphol. of **hydrazido**-functionalized derivs. of **hyaluronic acids** as hydrogels)

RN 1892-57-5 HCAPLUS
CN 1,3-Propanediamine, N'-(ethylcarbonimidoyl)-N,N-dimethyl- (9CI) (CA INDEX NAME)



RN 6066-82-6 HCAPLUS
CN 2,5-Pyrrolidinedione, 1-hydroxy- (9CI) (CA INDEX NAME)



RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **220650-37-3P 220650-43-1P 220650-45-3P**
RL: **RCT (Reactant)**; **SPN (Synthetic preparation)**;
PREP (Preparation); **RACT (Reactant or reagent)**
(preparation and surface morphol. of **hydrazido**-functionalized derivs. of **hyaluronic acids** as hydrogels)
RN 220650-37-3 HCAPLUS
CN Hyaluronic acid, 2-(4-hydrazino-1,4-dioxobutyl)hydrazide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 220650-43-1 HCAPLUS
CN Hyaluronic acid, 2-(6-hydrazino-1,6-dioxohexyl)hydrazide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 220650-45-3 HCAPLUS
CN Hyaluronic acid, 2-(8-hydrazino-1,8-dioxooctyl)hydrazide (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1998:527614** HCAPLUS
ED Entered STN: 21 Aug 1998
TI Synthesis and characterization of **photocrosslinkable** polysaccharide hydrogels.
AU Smeds, Kimberly A.; Pfister-Serres, Anne; Hatchell, Diane L.; Saloupis, Peter; Grinstaff, Mark W.
CS Department Chemistry, Duke University, Durham, NC, 27708, USA
SO Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (**1998**), PMSE-215 Publisher: American Chemical Society, Washington, D. C.
CODEN: 66KYA2
DT Conference; Meeting Abstract
LA English
AB Polysaccharide hydrogels are used for a number of medical and biotechnol. applications. One of the most thoroughly studied natural hydrogels are those composed of alginate, a natural polysaccharide. We have developed a modified **hyaluronic acid** (HA) biopolymer that can be **photocrosslinked** to form a stable hydrogel. **Hyaluronic acid**, a natural polysaccharide comprised of β(1-4) linked 2-acetamide-2-deoxy-D-glucose and β(1-3) linked D- **glucuronic acid**, is non-antigenic, non-inflammatory and non-tissue reactive. The phys., chemical and rheol. properties including the site and amount of modification of the polymer, the viscosity of the modified biopolymer, the stability of the biopolymer microcapsule, the solute diffusion characteristics, the mol. weight, and the biocompatibility of the polymer have been determined

L138 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:506274 HCAPLUS
DN 125:132818

ED Entered STN: 24 Aug 1996
TI Chemically modified **hyaluronates** for preventing scar formation after surgery
IN Obara, Takeo; Iso, Takako; Yamaguchi, Toshijiro; Hariki, Toshio; Yamaguchi, Michihiro
PA Shiseido Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 11 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K031-725
ICS A61K031-725
ICA C08B037-00; **C08B037-08**
CC 1-12 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 08157378	A2	19960618	JP 1994-341157	19941206 <--
	JP 3420851	B2	20030630		
PRAI	JP 1994-341157		19941206 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
JP 08157378	ICM	A61K031-725
	ICS	A61K031-725
	ICA	C08B037-00; **C08B037-08**

AB **Hyaluronates** modified by **crosslinking** with epoxy compds. at carboxyl group of its **glucuronic acid** linkage (**crosslinking** rate 0.5-5%) are claimed for preventing scar formation after surgery. The **hyaluronates** can be formulated into sheet- or film-like dosage forms. The inhibiting effects of the **hyaluronates** were tested in animal models.
ST **hyaluronate** epoxy **crosslinking** scar formation surgery
IT Keloid
Surgery
Wound
(chemical modified **hyaluronates** for preventing scar formation after surgery)
IT Epoxides
RL: RCT (Reactant); RACT (Reactant or reagent)
(chemical modified **hyaluronates** for preventing scar formation after surgery)
IT Pharmaceutical dosage forms
(films, chemical modified **hyaluronates** for preventing scar formation after surgery)
IT 2224-15-9, Ethylene glycol diglycidyl ether **9004-61-9**, **Hyaluronic acid**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(chemical modified **hyaluronates** for preventing scar formation after surgery)
IT **9004-61-9DP**, **Hyaluronic acid**, **crosslinking** derivs.
RL: **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(chemical modified **hyaluronates** for preventing scar formation after surgery)
IT **9004-61-9**, **Hyaluronic acid**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(chemical modified **hyaluronates** for preventing scar formation after surgery)
RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9004-61-9DP, Hyaluronic acid, crosslinking** derivs.
RL: **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(chemical modified **hyaluronates** for preventing scar formation after surgery)
RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:703616 HCAPLUS
DN 123:93165
ED Entered STN: 27 Jul 1995
TI The enhanced stability of the **crosslinked** hylan structure to **hydroxyl** (OH) radicals compared with the **uncrosslinked hyaluronan**
AU Al-Assaf, Saphwan; Phillips, Glyn O.; Deeble, D. J.; Parsons, Barry; Starnes, Hazel; Von Sonntag, C.
CS Newtech Innovation Centre, North East Wales Inst., Wrexham, Clwyd, LL13 7YP, UK
SO Radiation Physics and Chemistry (**1995**), 46(2), 207-17
CODEN: RPCHDM; ISSN: 0146-5724
PB Elsevier
DT Journal
LA English
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 14
AB A comparison was made of the relative stabilities of **hyaluronan** and hylan to degradation by OH radicals produced by γ-irradiation of aqueous solns. in N2O, when G (yield per 100 eV) for OH radicals is 5.6 and H atoms 0.6. Using low angle light scattering and viscometric methods, the change in mol. weight of the polysaccharides was measured with increasing dose. From the yield/dose curves (expressed as breaks per mol.), the initial G value for **hyaluronan** degradation is .apprx.4. A further slow post-irradiation decrease in mol. weight is observed, which can be brought to completion by incubating the solns. for 1 h at 60°.. Thereafter, the G value for degradation is .apprx.6. A similar post-irradiation degradation was found for hylan. A technique using tetranitromethane (TNM) was used to distinguish between 2 types of radicals formed on the **hyaluronan** backbone. Radicals of the 1-hydroxy-2-alkoxy type (C-2, C-4, C-2 and C3 of the **glucuronic acid**) would induce strand breakage by alkoxy elimination. For the equivalent alkoxy radical at C6 of the acetamido monosaccharide, ring opening would occur with formation of a hemi-acetal, leading also to strand breakage. The C-2 and C-3 radicals would eliminate water rather than produce breaks by β-alkoxy elimination. Thus, 3 out of the initially formed radicals would produce breaks by β-alkoxy formation. These can be stabilized with TNM and distinguished. These are the radicals involved in the post-irradiation thermal degradation process. Comparison of hylan and **hyaluronan** is, therefore, most valid when this post-irradiation process has been completed. Therefore, all G values for degradation were measured after incubation for 1 h at 60°. This investigation establishes the greater stability of hylan (G = 2) compared to hylan (G = 6). Therefore, in an environment such as supplementation of an inflamed joint where OH radicals are released, hylan is able to retain its integrity as a viscoelastic macromol. three times better than **hyaluronan.** Its potential as a viscosupplementation material, or as an inflammatory drug release matrix inserted within the joint is, therefore, greater than non-

crosslinked hyaluronan.
ST stability **crosslinking** hylan **hydroxyl** radical; **hyaluronan crosslinking** stability **hydroxyl** radical
IT Pharmaceutical dosage forms
(anti-inflammatory drug matrix; stability of **crosslinked** hylan to **hydroxyl** radicals)
IT Decomposition
Kinetics of decomposition
(stability of **crosslinked** hylan to **hydroxyl** radicals)
IT 3352-57-6, **Hydroxyl**, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(stability of **crosslinked** hylan to **hydroxyl** radicals)
IT **9004-61-9, Hyaluronan** 125935-84-4, Hylan
RL: **RCT (Reactant)**; THU (Therapeutic use); BIOL (Biological study); **RACT (Reactant or reagent)**; USES (Uses)
(stability of **crosslinked** hylan to **hydroxyl** radicals)
IT **9004-61-9, Hyaluronan**
RL: **RCT (Reactant)**; THU (Therapeutic use); BIOL (Biological study); **RACT (Reactant or reagent)**; USES (Uses)
(stability of **crosslinked** hylan to **hydroxyl** radicals)
RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:536511 HCAPLUS
DN 121:136511
ED Entered STN: 17 Sep 1994
TI Novel Hydrogels of **Hyaluronic Acid**: Synthesis, Surface Morphology, and Solid-State NMR
AU Pouyani, Tara; Harbison, Gerard S.; Prestwich, Glenn D.
CS Department of Chemistry, SUNY, Stony Brook, NY, 11794-3400, USA
SO Journal of the American Chemical Society (**1994**), 116(17), 7515-22
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA English
CC 44-7 (Industrial Carbohydrates)
AB A convenient methodol. was developed that allowed the attachment of pendent **hydrazido** groups to the **glucuronate** moieties of **hyaluronic acid** (I). This methodol. was extended to high mol. weight I (1.5 + 106), and the products were **crosslinked** with four homobifunctional **activated esters** to give novel I hydrogels. Solid-state 13C NMR using cross-polarization and magic angle spinning revealed that the lyophilized native I and **hydrazido** I retained solution-like structures in the solid state. The four I hydrogels showed significant structural changes relative to native I, and the carbon resonances of the **crosslinkers** were clearly evident. The surface morphologies of these **crosslinked** I derivs. were examined using SEM. The electron micrographs of the freeze-dried hydrogels showed the presence of regular sheetlike structures forming pores (20-50 μm). In contrast, native I showed predominantly fibrous and irregular structures.
ST **hyaluronate** hydrogel **azide crosslinked**
IT Nuclear magnetic resonance
(of **hyaluronate** hydrogels)
IT Polymer morphology

(surface, of **hyaluronate** hydrogels)

IT **156464-77-6P 156464-78-7P 156464-79-8P 156464-80-1P**
RL: **PREP (Preparation)**
(hydrogels, preparation and NMR spectra of)

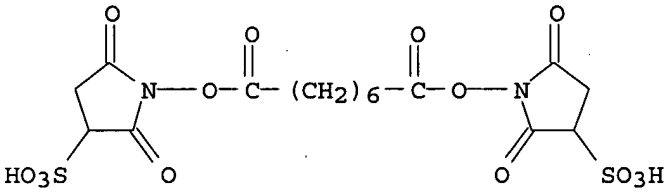
IT **156464-81-2P**
RL: **RCT (Reactant)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**; **RACT (Reactant or reagent)**
(preparation and **crosslinking** of)

IT **156464-77-6P 156464-78-7P 156464-79-8P 156464-80-1P**
RL: **PREP (Preparation)**
(hydrogels, preparation and NMR spectra of)

RN 156464-77-6 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with disodium 1,1'[(1,8-dioxo-1,8-octanediyl)bis(oxy)]bis[2,5-dioxo-3-pyrrolidinesulfonate] and hexanedioic acid dihydrazide (9CI) (CA INDEX NAME)

CM 1

CRN 127634-19-9
CMF C16 H20 N2 O14 S2 . 2 Na



●2 Na

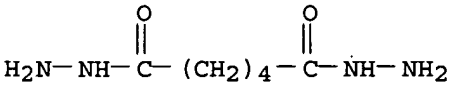
CM 2

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 3

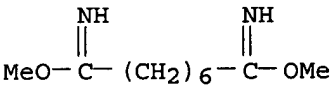
CRN 1071-93-8
CMF C6 H14 N4 O2



RN 156464-78-7 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with dimethyl octanediimidate and hexanedioic acid dihydrazide (9CI) (CA INDEX NAME)

CM 1

CRN 29878-26-0
CMF C10 H20 N2 O2



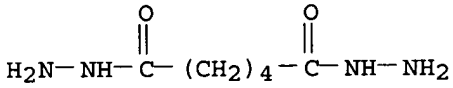
CM 2

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 3

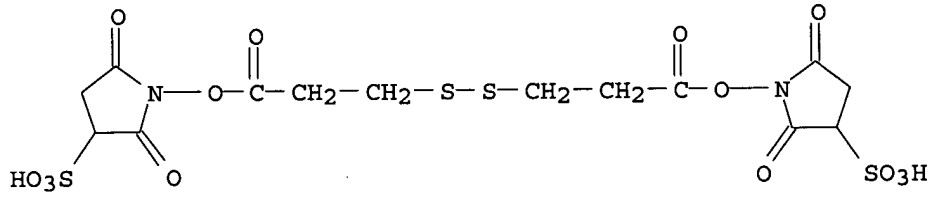
CRN 1071-93-8
CMF C6 H14 N4 O2



RN 156464-79-8 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with disodium 1,1'-[dithiobis[(1-oxo-3,1-propanediyl)oxy]]bis[2,5-dioxo-3-pyrrolidinesulfonate] and hexanedioic acid dihydrazide (9CI) (CA INDEX NAME)

CM 1

CRN 142702-31-6
CMF C14 H16 N2 O14 S4 . 2 Na



●2 Na

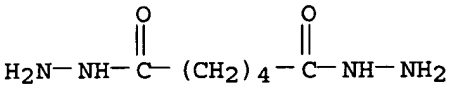
CM 2

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 3

CRN 1071-93-8
CMF C6 H14 N4 O2

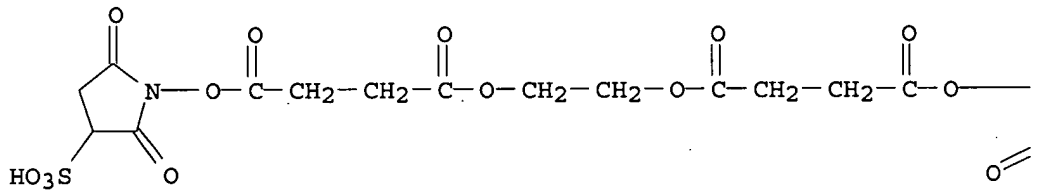


RN 156464-80-1 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with 1,1'-(1,2-ethanediyl) bis[4-[(2,5-dioxo-3-sulfo-1-pyrrolidinyl)oxy]-4-oxobutanoate] disodium salt and hexanedioic acid dihydrazide (9CI) (CA INDEX NAME)

CM 1

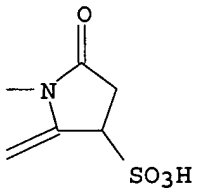
CRN 142702-32-7
CMF C18 H20 N2 O18 S2 . 2 Na

PAGE 1-A



●2 Na

PAGE 1-B



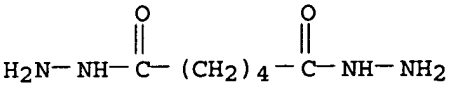
CM 2

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 3

CRN 1071-93-8
CMF C6 H14 N4 O2



IT **156464-81-2P**
RL: **RCT (Reactant)**; **SPN (Synthetic preparation)**; **PREP (Preparation)**; **RACT (Reactant or reagent)**
(preparation and **crosslinking** of)
RN 156464-81-2 HCAPLUS
CN Hyaluronic acid, sodium salt, polymer with hexanedioic acid dihydrazide (9CI) (CA INDEX NAME)

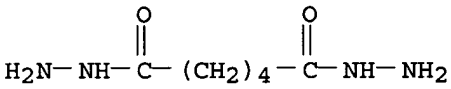
CM 1

CRN 9067-32-7
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

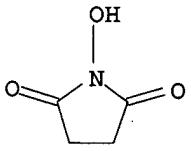
CRN 1071-93-8
CMF C6 H14 N4 O2



L138 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:483790 HCAPLUS
DN 121:83790
ED Entered STN: 20 Aug 1994
TI Functionalized Derivatives of **Hyaluronic Acid** Oligosaccharides: Drug Carriers and Novel Biomaterials
AU Pouyani, Tara; Prestwich, Glenn D.
CS Department of Chemistry, University at Stony Brook, Stony Brook, NY, 11794-3400, USA
SO Bioconjugate Chemistry (**1994**), 5(4), 339-47
CODEN: BCCHES; ISSN: 1043-1802
DT Journal
LA English
CC 33-4 (Carbohydrates)
Section cross-reference(s): 63
AB Oligosaccharides derived from **hyaluronic acid** (HA), a naturally occurring linear polysaccharide composed of repeating disaccharide units of N-acetyl-D-glucosamine and D-**glucuronic acid**, can be chemical modified to introduce a pendant **amine** -like functionality (patent application pending). Covalent attachment of steroidal and nonsteroidal antiinflammatory drugs to functionalized HA oligosaccharides was accomplished with the incorporation of hydrolytically labile bonds. Further derivatization of the pendant group with homobifunctional **crosslinkers** allowed the introduction of covalent **crosslinks.** Chemical-modified HA oligosaccharides were unambiguously characterized in solution by high-resolution 1H NMR spectroscopy.
ST **hyaluronic acid** functionalized drug deriv
IT **9004-61-9D**, **Hyaluronic acid**, derivs.
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**

(functionalized, as drug carriers, preparation of)
IT 70880-27-2P 104400-52-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction with **hyaluronic acid** oligosaccharide)
IT 155021-43-5P 155021-44-6P 155021-45-7P 155021-46-8P 155021-47-9P
155021-48-0P 155021-49-1P 155021-50-4P 155021-51-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
IT 1071-93-8, Adipic **dihydrazide** 4146-43-4, Succinic **dihydrazide** 20247-84-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of with **hyaluronic acid** oligosaccharide)
IT 2203-97-6, Hydrocortisone hemisuccinate 15687-27-1, Ibuprofen
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of with hydroxysuccinimide)
IT **9004-61-9D**, **Hyaluronic acid**, sugar derivs.
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(reaction of, with dicarboxylic acid **hydrazides**)
IT **6066-82-6**, **N-Hydroxysuccinimide**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with ibuprofen or hydrocortisone hemisuccinate)
IT **9004-61-9D**, **Hyaluronic acid**, derivs.
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(functionalized, as drug carriers, preparation of)
RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(reaction of, with dicarboxylic acid **hydrazides**
IT **6066-82-6**, **N-Hydroxysuccinimide**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with ibuprofen or hydrocortisone hemisuccinate)
RN 6066-82-6 HCAPLUS
CN 2,5-Pyrrolidinedione, 1-hydroxy- (9CI) (CA INDEX NAME)



L138 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1994:477686 HCAPLUS
DN 121:77686
ED Entered STN: 20 Aug 1994
TI Biotinylated **Hyaluronic Acid**: A New Tool for Probing **Hyaluronate**-Receptor Interactions
AU Pouyani, Tara; Prestwich, Glenn D.
CS Department of Chemistry, University at Stony Brook, Stony Brook, NY, 11794-3400, USA
SO Bioconjugate Chemistry (**1994**), 5(4), 370-2
CODEN: BCCHES; ISSN: 1043-1802
DT Journal
LA English
CC 9-15 (Biochemical Methods)
Section cross-reference(s): 6
AB **Hyaluronic acid** (HA) is a linear polysaccharide

composed of repeating disaccharide units of D-**glucuronic acid** (GlcUA) and N-acetyl-D-glucosamine (GlcNAc). **Hyaluronate** plays an important role in many biol. processes as mediated by its interactions with a number of HA-binding proteins (the "hyaladherins") and with the cell surface HA-receptor, CD44. Studies of **hyaluronate**-hyaladherin interactions would be greatly facilitated by the availability of mol. probes derived from HA. The authors recently reported a convenient chemical modification of **hyaluronate** that introduces multiple pendant **amine** functionalities onto the HA carboxylate residues. The authors now report the preparation of biotinylated **hyaluronic acid** (mol. weight = 1.2+106 Da) as a probe for histochem. and immunochem. characterization of HA-binding proteins. Approx. one-third of the available HA **glucuronate** residues could be readily biotinylated in high mol. weight HA.

ST biotinylated **hyaluronate** probe binding protein

IT Biotinylation
(of **hyaluronic acid**)

IT **Proteins, specific or class**
RL: ANST (Analytical study)
(**hyaluronate**-binding, biotinylated **hyaluronic acid** as probe for)

IT **9004-61-9**, **Hyaluronic acid**
RL: PROC (Process)
(biotinylation of)

IT **9004-61-9DP**, **Hyaluronic acid**, biotinylated
RL: **PREP (Preparation)**
(preparation of, application as probe for **hyaluronate**-binding protein in relation to)

IT **9004-61-9**, **Hyaluronic acid**
RL: PROC (Process)
(biotinylation of)

RN 9004-61-9 HCAPLUS

CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **9004-61-9DP**, **Hyaluronic acid**, biotinylated
RL: **PREP (Preparation)**
(preparation of, application as probe for **hyaluronate**-binding protein in relation to)

RN 9004-61-9 HCAPLUS

CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1992:449109 HCAPLUS

DN 117:49109

ED Entered STN: 08 Aug 1992

TI Solid-state NMR of N-acylureas derived from the reaction of **hyaluronic acid** with isotopically-labeled **carbodiimides**

AU Pouyani, Tara; Kuo, Jing Wen; Harbison, Gerard S.; Prestwich, Glenn D.

CS Dep. Chem., State Univ. New York, Stony Brook, NY, 11794-3400, USA

SO Journal of the American Chemical Society (**1992**), 114(15), 5972-6
CODEN: JACSAT; ISSN: 0002-7863

DT Journal

LA English

CC 33-8 (Carbohydrates)
Section cross-reference(s): 22

AB **Hyaluronic acid** (HA) is a naturally-occurring linear polysaccharide consisting of alternating D-**glucuronic acid** and N-acetyl-D-glucosamine residues. Reaction of the carboxyl group of the **glucuronate** residues with

1-ethyl-3-(3-(dimethylamino)propyl)**carbodiimide** (EDC) in the presence of **primary amines** yielded only the N-acylurea adducts rather than the expected amide coupling products. To determine the nature of this linkage unambiguously and to deduce the **primary** structure of the N-acylurea products, 13C- and 15N-labeled 1-ethyl-3-(3-(dimethylamino)propyl)**carbodiimide** were synthesized. The isotopically-labeled **carbodiimides** were coupled to the carboxyl group of HA (mol. size ca. 2000000 Da) in water at pH = 4.75. The modified polysaccharides were then isolated, purified, and examined by cross polarization and magic angle spinning (CP-MAS) solid-state 13C and 15N NMR. The chemical shifts and states of protonation of the nitrogens confirmed the presence of two isomeric N-acylureas in unequal amts. and ruled out the presence of any unrearranged O-acylurea product.

ST urea **hyaluronic acid** solid state NMR; polysaccharide acylurea solid state NMR; labeled **carbodiimide** coupling **hyaluronic acid**

IT Nuclear magnetic resonance
(of N-acylurea haluronic acid)

IT Polysaccharides, properties
RL: SPN (Synthetic preparation); PREP (Preparation)
(acidic, N-acylurea haluronic, preparation and solid-state NMR spectra of)

IT 84051-02-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with (dimethylamino)propyl isothiocyanate)

IT 463-71-8, Thiophosgene
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with (dimethylamino)propylamine)

IT 109-55-7, 3-(N,N-Dimethylamino)propylamine
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with labeled Et isothiocyanate)

IT **9004-61-9, Hyaluronic acid**
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(coupling of, with **carbodiimides**)

IT 141727-00-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and condensation of, with (dimethylamino)propylamine)

IT 141727-02-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and condensation of, with haluronic acid)

IT 27421-70-1P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and condensation of, with labeled ethylamine)

IT 141727-04-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and coupling of, with haluronic acid)

IT 141727-01-7P 141727-03-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with mercury(II) oxide)

IT 141727-02-8DP, haluronic acid derivative 141727-04-0DP, haluronic acid derivative
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and solid-state NMR spectra of)

IT 30860-31-2, Carbon-13C disulfide
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in synthesis of **carbodiimides**)

IT 79-22-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with urea derivative)

IT **9004-61-9, Hyaluronic acid**
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(coupling of, with **carbodiimides**)

RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 17 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1992:414416** HCAPLUS
DN **117:14416**
ED Entered STN: 11 Jul 1992
TI Manufacture of pharmaceutical-**hyaluronic acid** complexes
IN Akima, Kazuo; Iwata, Yuhei; Matsuo, Kayoko; Watari, Nobutoshi
PA Shiseido Co., Ltd., Japan
SO PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM A61K047-48
ICS A61K031-725
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9206714	A1	19920430	WO 1991-JP1431	19911018	<--
	W: AU, CA, JP, US					
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE					
	CA 2070672	AA	19920419	CA 1991-2070672	19911018	<--
	CA 2070672	C	20021008			
	AU 9187140	A1	19920520	AU 1991-87140	19911018	<--
	AU 652784	B2	19940908			
	EP 506976	A1	19921007	EP 1991-917837	19911018	<--
	EP 506976	B1	19970409			
	R: DE, FR, GB, IT, NL					
	US 5733891	A	19980331	US 1995-380324	19950130	<--
PRAI	JP 1990-280628	A	19901018	<--		
	JP 1991-159611	A	19910603	<--		
	WO 1991-JP1431	A	19911018	<--		
	US 1992-861852	B1	19920618	<--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 9206714	ICM	A61K047-48	
	ICS	A61K031-725	
EP 506976	ECLA	A61K047/48K8	<--
US 5733891	NCL	514/059.000; 514/034.000; 536/006.400; 536/018.500; 536/055.100	
	ECLA	A61K047/48K8	<--

AB Pharmaceuticals are bound to carboxyl groups of **glucuronic acid** residues of **hyaluronic acid** via amido linkage. The pharmaceuticals may be neoplasm inhibitors. Thus, Na **hyaluronate** in pyridine was converted to N-hydroxysuccinimidated **hyaluronic acid** which was then treated with mitomycin C to give a mitomycin C-**hyaluronic acid** complex. The complex has less side effects than mitomycin C itself, and is delivered to the target more efficiently.
ST **hyaluronate** neoplasm inhibitor complex; mitomycin **hyaluronate** complex prepn
IT Neoplasm inhibitors
(complexes with **hyaluronate** as)
IT 50-07-7D, Mitomycin C, complexes with **hyaluronic acid**
51-21-8D, 5-Fluorouracil, complexes with **hyaluronic acid**
147-94-4D, Cytosinearabinoside, complexes with **hyaluronic**

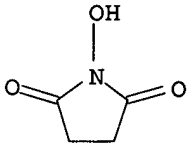
acid 20830-81-3D, Daunomycin, complexes with **hyaluronic acid** 56420-45-2D, Epirubicin, complexes with **hyaluronic acid**
RL: BIOL (Biological study)
(as neoplasm inhibitors)

IT **6066-82-6**, **N-Hydroxysuccinimide**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with sodium **hyaluronate** and ethyl(dimethylaminopropyl)**carbodiimide**)

IT **1892-57-5**, 1-Ethyl-3-(3-dimethylaminopropyl)**carbodiimide**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with sodium **hyaluronate** and hydroxysuccinimide)

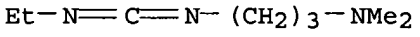
IT **6066-82-6**, **N-Hydroxysuccinimide**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with sodium **hyaluronate** and ethyl(dimethylaminopropyl)**carbodiimide**)

RN 6066-82-6 HCAPLUS
CN 2,5-Pyrrolidinedione, 1-hydroxy- (9CI) (CA INDEX NAME)



IT **1892-57-5**, 1-Ethyl-3-(3-dimethylaminopropyl)**carbodiimide**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with sodium **hyaluronate** and hydroxysuccinimide)

RN 1892-57-5 HCAPLUS
CN 1,3-Propanediamine, N'-(ethylcarbonimidoyl)-N,N-dimethyl- (9CI) (CA INDEX NAME)



L138 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:472102 HCAPLUS
DN 115:72102
ED Entered STN: 23 Aug 1991
TI Chemical modification of **hyaluronic acid** by **carbodiimides**
AU Kuo, Jing Wen; Swann, David A.; Prestwich, Glenn D.
CS Dep. Chem., State Univ. New York, Stony Brook, NY, 11794-3400, USA
SO Bioconjugate Chemistry (**1991**), 2(4), 232-41
CODEN: BCCHES; ISSN: 1043-1802
DT Journal
LA English
CC 33-8 (Carbohydrates)
AB **Hyaluronic acid** (HA) is a linear polysaccharide with repeating disaccharide units of **glucuronic acid** and N-acetylglucosamine and is found in the extracellular matrix of connective tissues. Reaction of high mol. weight sodium **hyaluronate** (NaHA, MW .apprx.2 x 106) with **carbodiimides** gave the N-acylurea and O-acylisourea as NaHA-**carbodiimide** adducts. None of the expected intermol. coupling with the **amine** component was observed On the basis of this new observation, this method for chemical modification of HA was used in conjunction with new synthetic **carbodiimides** to prepare HA derivs. bearing lipophilic, aromatic, **cross-linked**, and tethered **functional groups.** The

degree of conversion to NaHA-acylurea products appears to depend upon both the characteristics of various **carbodiimides** and the conformational structure of NaHA.

ST **carbodiimide** prepn coupling polysaccharide; **hyaluronic acid** acylurea adduct; uronic hyal acid acylurea adduct; urea acyl adduct **hyaluronic acid**

IT **Carbodiimides**
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling reaction of, with **hyaluronic acid**)

IT Polysaccharides, reactions
RL: SPN (Synthetic preparation); PREP (Preparation)
(**hyaluronic acid** derivs., preparation of)

IT Coupling reaction
(of **hyaluronic acid** with **carbodiimides**)

IT 124-09-4, 1,6-Hexanediamine, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(amidation of)

IT 542-85-8, Ethyl isothiocyanate
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with **amines**)

IT 106-50-3, 1,4-Benzenediamine, reactions 2432-74-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling of, with Et isothiocyanate)

IT **9067-32-7**, Sodium **hyaluronate**
RL: **RCT (Reactant)**; **RACT (Reactant or reagent)**
(coupling of, with **carbodiimides**)

IT 134736-14-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and amidation of)

IT 134736-08-6P 134736-09-7P 134736-11-1P 134736-12-2P 134736-16-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and coupling of, with sodium **hyaluronate**)

IT 62552-50-5P 70498-33-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and elimination reaction of, **carbodiimide** from)

IT 134736-17-7DP, **hyaluronic acid** derivative
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)

IT 16349-59-0P 87257-24-7P 134736-06-4P 134736-07-5P 134736-15-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and oxidative elimination reaction of, **carbodiimide** from)

IT 66095-18-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with alkyl isothiocyanates)

IT 134736-04-2P 134736-05-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with sodium **hyaluronate**)

IT 134736-03-1DP, **hyaluronic acid** ester derivative
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and rearrangement of)

IT 134736-13-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reduction of)

IT 96874-50-9DP, **hyaluronic acid** derivative 134736-03-1DP,
hyaluronic acid amide derivative 134736-10-0DP,
hyaluronic acid derivative 134736-18-8DP,
hyaluronic acid derivative 134736-19-9DP,
hyaluronic acid derivative 134736-20-2DP,
hyaluronic acid derivative 134736-21-3DP,
hyaluronic acid derivative 134736-22-4DP,
hyaluronic acid derivative
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
IT 111-86-4, 1-Octanamine 2869-34-3, 1-Tridecanamine
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with Et isothiocyanate)
IT 27421-70-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with **amine**)
IT **9004-61-9, Hyaluronic acid**
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(reaction of, with **carbodiimides**)
IT **9067-32-7**, Sodium **hyaluronate**
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(coupling of, with **carbodiimides**)
RN 9067-32-7 HCAPLUS
CN Hyaluronic acid, sodium salt (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **9004-61-9, Hyaluronic acid**
RL: **RCT (Reactant); RACT (Reactant or reagent)**
(reaction of, with **carbodiimides**)
RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L138 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **1963:9792** HCAPLUS
DN **58:9792**
OREF 58:1665h,1666a-c
ED Entered STN: 22 Apr 2001
TI Isolation of **hyaluronate**-protein complex from human synovial fluid
AU Sandson, John; Hamerman, David
CS Albert Einstein Coll. Med., New York
SO Journal of Clinical Investigation (**1962**), 41, 1817-30
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA Unavailable
CC 56 (General Biochemistry)
AB Mild methods were used to isolate **hyaluronate** from large vols. of pooled normal human synovial fluid. **Hyaluronate** containing about 2% protein was isolated by a combination of adsorption, ultrafiltration, and ultracentrifugation. These isolation procedures were sufficiently mild so that the final product had an intrinsic viscosity similar to the starting synovial fluid, and possessed anomalous viscosity. A similar product was obtained from synovial fluids by zone electrophoresis at pH 5.4. and adsorption. Evidence that **hyaluronate** and protein were firmly combined led to use of the term **hyaluronate**-protein (HP). With I131-labeled HP zone electrophoresis over a pH range of 11.2 to 3.5 showed migration of **hyaluronate** (measured as hex-uronic acid) and protein (measured by radioactivity) as a single peak toward the anode. Neither high salt concentration, urea, nor addition of a basic protein dissociated **hyaluronate** from protein. After exhaustive digestion of HP with

bacterial **hyaluronidase** and dialysis, 6-7% nondialyzable **hyaluronate** remained bound to all the protein. This indicates that **hyaluronate** is bound to protein by chemical bonds not susceptible to bacterial **hyaluronidase** digestion. Further digestion of the nondialyzable residue with a liver enzyme containing β-**glucuronidase** and β-glucosaminidase removed hex-uronic acid and acetylglucosamine units of **hyaluronate.** Treatment of HP with hydrazine led to formation of 1.3 μmol of nondialyzable **hydrazide** or hydrazone/HP. Some evidence suggests that ester bonds were split and a **hydrazide** formed. If hydrazine treatment broke ester bonds, such bonds might be formed through COO- groups of **hyaluronate** and OH groups of serine or threonine, through COO- groups of dicarboxylic amino acids and OH groups of **hyaluronate**, or through terminal COO- groups of an amino acid and OH groups of **hyaluronate.** Comparison of HP with chondromucoprotein (CMP) isolated from bovine nasal cartilage shows that unlike HP, CMP contains about 25% protein firmly bound to chondroitin sulfate. Like HP, the protein of CMP contains a high proportion of dicarboxylic amino acids and serine, and may be combined in ester linkage with part of the acidic groups of chondroitin sulfate, since these links are disrupted by prolonged incubation in alkali. The effects of proteolytic enzymes point out major differences in the structure of CMP and HP. **Hyaluronate** chains are probably much longer and occupy a domain that is even larger than their actual size. Interpretation or overlap of these highly solvated mols., even at low concentration, accounts for the extremely high viscosity and shear-dependent viscosity of **hyaluronate** solns. This suggests that **hyaluronate** may exist as an uninterrupted long-chain polymer with protein present as side chains, or at the end(s) of the **hyaluronate** mol.

IT **Proteins**
(**hyaluronic acid** complexes, separation from synovial fluid)

IT Synovial fluid
(**hyaluronic acid**-protein complex of, separation of)

IT human
(isolate **hyaluronate** from synovial fluid)

IT **9004-61-9, Hyaluronic acid**
(protein complex, separation from synovial fluid, from Rous sarcoma, amino acids in)

IT **9004-61-9, Hyaluronic acid**
(protein complex, separation from synovial fluid, from Rous sarcoma, amino acids in)

RN 9004-61-9 HCAPLUS
CN Hyaluronic acid (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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(FILE 'HCAPLUS' ENTERED AT 12:42:37 ON 04 MAY 2005)
DEL HIS

FILE 'REGISTRY' ENTERED AT 12:42:56 ON 04 MAY 2005
L1 1366 S HYALURONIC ACID OR ?HYALURON?/CNS
L2 2 S GLUCURONIC ACID/CN
L3 1 S L-GLUCURONIC ACID/CN
E C6H10O7/MF
L4 36 S E3 AND OC5/ES
SEL RN 5-7 9 12-15 21 22
L5 26 S L4 NOT E1-E10

FILE 'HCAPLUS' ENTERED AT 12:48:14 ON 04 MAY 2005

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L6        16955 S L1
L7        23468 S HYALURONIC ACID OR ?HYALURON?
L8        24208 S L6,L7
L9         5792 S L2,L3,L5
L10       11520 S GLUCURONIC ACID
L11         622 S L8 AND L9,L10
L12           1 S (US20040072793 OR US6630457)/PN OR (US2003-680000# OR WO99-US
                E AESCHLIMAN/AU
L13          20 S E5,E7
L14          31 S E22-E25
                E ASCHLIMAN/AU
L15          15 S E8
                E BULPITT P/AU
L16           6 S E4-E6
                E ORTHOGEN/PA,CS
                E ORTHOGE/PA,CS
L17          13 S E5-E26,E28-E33
L18           5 S L8 AND L13-L17
L19           1 S L12 AND L8
L20           5 S L18,L19
L21           2 S L9,L10 AND L20
L22           2 S L20 AND L11
L23           5 S L20-L22
L24         210 S A61K031-728/IPC
L25        1394 S C08B037-08/IPC
L26         373 S (C08L005-08 OR C09D105-08 OR C09J105-08)/IPC
L27       25580 S L8,L24-L26
L28         628 S L27 AND L9,L10
L29        1082 S L27 AND ?GLUCURON?
L30        1128 S L11,L28,L29
L31         891 S L30 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
L32           2 S L30 AND NUCLEOPHIL?
L33           8 S L30 AND FUNCTIONAL GROUP
                E FUNCTIONAL GROUP/CT
L34          12 S L30 AND E10+OLD,NT,PFT,RT
                E NUCLEOPHIL/CT
L35           1 S L32 AND L33,L34
L36         975 S HOBT
L37        1369 S NHS
L38         201 S HYDROXYSULFOSUCCINIMIDE
L39        5727 S N HYDROXYSUCCINIMIDE
L40        3249 S HYDROXYBENZOTRIAZOLE
L41          35 S SULFOSUCCINIMIDE
L42       22211 S NITROPHENOL
L43         976 S M NITROPHENOL
L44        2098 S O NITROPHENOL
L45        8575 S P NITROPHENOL
L46        1188 S PENTAFLUOROPHENOL
L47           6 S PERHALOPHENOL
L48           3 S PHENOL(L)PERHALO
L49          20 S PHENOL(L)PERHALO?
L50        4474 S HALOGEN?(L)PHENOL
L51       62651 S ?TRIAZOL?
L52       13552 S MALEIMIDE
L53       23140 S SULFHYDRYL
L54       32341 S HYDRAZID?
L55      112201 S ?AZIDE?
L56      532074 S ?ALDEHYD?
L57        4023 S ACTIV? ESTER?
L58      390371 S AMINE
L59      182700 S AMMONIA
L60       46505 S (PRIMARY OR SECONDARY)(L)AMINE
L61      109435 S HYDROXYL
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L62          57 S L31 AND L36-L61

     FILE 'REGISTRY' ENTERED AT 13:22:33 ON 04 MAY 2005
L63           1 S 82436-78-0
L64           3 S 100-02-7 OR 88-75-5 OR 554-84-7
L65          58 S C6H5NO3/MF AND C6/ES AND NITRO
L66           2 S L65 AND IDS/CI
L67           1 S 108-95-2
L68           1 S 771-61-9
L69           1 S 2592-95-2
L70           1 S 6066-82-6
L71           8 S L63,L64,L67-L70

     FILE 'HCAPLUS' ENTERED AT 13:25:11 ON 04 MAY 2005
L72           7 S L71 AND L31
L73          59 S L62,L72
L74           0 S L73 AND CYTOKIN?
L75           3 S L73 AND ?PEPTIDE?
L76           0 S L73 AND RGD
L77           0 S L73 AND APPQQEA
                E RGD/CT
L78           0 S L73 AND E7+OLD,NT,PFT,RT
                E E7+ALL
L79           8 S L73 AND E1+NT
L80           2 S L73 AND E1+OLD
L81           2 S L73 AND E1+PFT
L82           9 S L73 AND E1+RT
L83           2 S L73 AND GROWTH FACTOR
                E GROWTH FACTOR/CT
L84           1 S L73 AND E14+OLD,NT,PFT,RT
L85           3 S L73 AND E34+OLD,NT,PFT,RT
                E TGF/CT
                E E11+ALL
                E TRANSFORMING GROWTH FACTOR/CT
                E E6+ALL
L86           0 S L73 AND E2
                E TRANSFORMING GROWTH FACTOR/CT
L87           0 S L73 AND E24+OLD,NT,PFT,RT
L88           0 S L73 AND E43+OLD,NT,PFT,RT
L89           0 S L73 AND E44-E51
L90           0 S L73 AND BMP
L91           0 S L73 AND BONE MORPHO? PROTEIN
                E BONE MORPHOG/CT
                E E4+ALL
L92           0 S L73 AND E2+OLD,NT,PFT,RT
                E CYTOKINES/CT
L93           7 S L73 AND E3+OLD,NT,PFT,RT
L94          14 S L74-L93
L95          26 S L30 AND (?CROSSLINK? OR ?CROSS LINK?)
                E CROSSLINK/CT
L96          25 S L30 AND (E4+OLD,NT,PFT,RT OR E15+OLD,NT,PFT,RT OR E39+OLD,NT,
L97           3 S L30 AND E49+OLD,NT,PFT,RT
L98           3 S L30 AND E61+OLD,NT,PFT,RT
L99           3 S L30 AND E63+OLD,NT,PFT,RT
L100         44 S L95-L99
L101         24 S L100 AND L31
L102          6 S L101 AND L32-L62,L72-L94
L103         11 S L30 AND ?CARBODIIMID?
L104          0 S L30 AND ?CARBO DIIMID?
                E CARBODIIMIDE/CT
L105          8 S L30 AND E6+OLD,NT,PFT,RT
L106          1 S L103,L104 AND L101
L107         42 S L101,L102,L103,L105,L106,L23
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L108          90 S L94,L107,L73
L109          12 S L1(L)PREP+NT/RL AND L108
L110           7 S L1/DP AND L108
L111          15 S L109,L110,L23
L112          16 S L1 (L) RACT+NT/RL AND L108
L113          24 S L111,L112
L114          24 S L113 AND L6-L62,L72-L113
L115          90 S L108 AND L6-L62,L72-L113
L116          24 S L114 AND L115
                 SEL DN AN 5 7 10-12 15 19 20 23 24
L117          14 S L116 NOT E1-E30
L118          66 S L115 NOT L116
                 SEL DN AN 3 13 24 50
L119           4 S L118 AND E31-E40
L120          18 S L117,L119
L121          19 S L120,L23
                 SEL RN

     FILE 'REGISTRY' ENTERED AT 13:57:59 ON 04 MAY 2005
L122         217 S E42-E258
L123         218 S E41 OR L122
L124          25 S L123 AND L1
L125           0 S L123 AND L2,L3,L5
L126           3 S L123 AND L63,L65,L66-L71
L127         209 S TRANSGLUTAMINASE

     FILE 'HCAPLUS' ENTERED AT 14:01:19 ON 04 MAY 2005
L128           1 S L127 AND L121
L129           1 S L121 AND TRANSGLUTAMINASE
L130          19 S L128,L121,L129

     FILE 'REGISTRY' ENTERED AT 14:02:27 ON 04 MAY 2005
L131           1 S L123 AND L127
L132         189 S L123 NOT L124,L126,L131
L133           3 S L132 AND SQL/FA
L134          63 S L132 AND UNSPECIFIED
L135           1 S L134 AND INCERT
L136           1 S L134 AND SEPRAFILM

     FILE 'HCAPLUS' ENTERED AT 14:05:37 ON 04 MAY 2005
L137           1 S L135,L136 AND L130
L138          19 S L130,L137

     FILE 'REGISTRY' ENTERED AT 14:05:58 ON 04 MAY 2005
L139         123 S L132 NOT L133,L134

     FILE 'HCAPLUS' ENTERED AT 14:08:06 ON 04 MAY 2005

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